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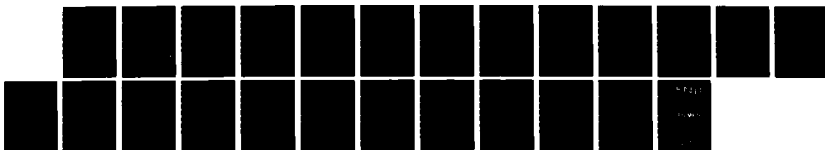
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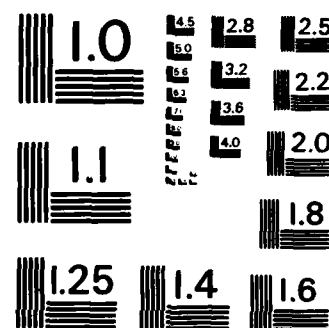
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Seventh European Immunology Congress,
Jerusalem, Israel

Claire E. Zomzely-Neurath

22 November 1985

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SEVENTH EUROPEAN IMMUNOLOGY CONGRESS,
JERUSALEM, ISRAEL

1 INTRODUCTION

The Seventh European Immunology Congress was held in Jerusalem at the Binyanei Ha'ooma Convention Center from 8 through 13 September 1985. The attendance was quite large, about 1100 participants. Most of the attendees were from Israel, the UK, and Europe, although there were a fair number of participants from the US. There were 65 exhibitions representing companies from Israel, Europe, the UK, and the US with displays of scientific equipment and products geared to the field of immunology research. The meeting covered a wide range of topics and consisted of symposia and colloquia (the format is shown in Table 1). In addition, there were 30 workshops, which consisted of discussions of the poster presentations in the various research categories as outlined in Table 1. A total of 598 posters were presented for viewing and discussion.

Scientists from 27 countries presented their research in the various sessions of the immunology meeting. French scientists dominated the sessions with a total of 154 presentations, indicating a major thrust in immunology research in France. Israel was represented by 142 papers--the large number due partly to the fact that the meeting was held in Israel, but also due to a major emphasis on immunology research during the past few years (see ONR, London report R-6-85). Although this was a European meeting, there were 76 presentations by US scientists. Surprisingly, Poland, Hungary, and Yugoslavia were represented by an average of 16 presentations per country, indicating an increasing emphasis on immunology research in these countries.

Of particular interest to participants at the meeting, as judged by attendance at the various sessions, were the reports dealing with interferons and interleukines; immunoregulation; immune, endocrine, and neural research

systems-correlations and interactions; immunodeficiency; as well as immunomodulation and immunopharmacology. Although there were excellent sessions on the wide variety of topics shown in Table 1, it is not possible to cover all the sessions in this report. Therefore, only the above-mentioned research areas in immunology will be presented.

2 INTERFERONS AND INTERLEUKINES

J. Van Damme and coworkers (Laboratory of Virology, The Rega Institute, Faculty of Medicine, University of Leuven, Belgium) reported on the purification of the partial sequencing of a factor, termed 22k, which exhibited an antiviral effect. This 22k polypeptide was obtained by *in vitro* stimulation of mononuclear cells from human peripheral blood with mitogens that cause the release of factors (monokines and lymphokines) which possess distinct biological activities. The 22k factor can induce production of human β -interferon (HuIFN- β) in cultured human fibroblasts, thereby rendering these cells resistant to viral infection. In addition to an antiviral effect, the pure protein exhibits several other biological activities. Most significant was the finding that intravenous injection of the factor in rabbits caused fever and granulopenia at doses of 0.1 to 1 μ g/kg, effects attributed to a monokine called endogenous pyrogen (EP). *In vitro*, the protein was scored as positive in a lymphocyte-activating factor assay (LAF) at very low doses. LAF and EP are considered to be members of one family of monokines called interleukin-1 (IL-1). For this reason, and because the amino acid sequence of the 22k factor is at least partially homologous to a complementary DNA-derived IL-1 sequence, Van Damme et al. postulated that the 22k factor also belongs to the IL-1 family.

A. Altman (Scripps Clinic and Research Foundation, La Jolla, California) presented an interesting report on the use of synthetic peptides derived from interleukin 2 (IL-2) and antibodies as probes for detection and structure-function analysis. IL-2 is a T-cell derived

Table 1

Format of the Seventh European Immunology Meeting

Opening Plenary Session--Chairman: M. Sela, Israel

Structural and functional analysis of Class II MHC molecules, H.O. McDevitt, US

The role of cloned lymphokines in B-cell activation, G. Nossal, Australia.

Symposia

Molecular biology, genetics, and function of MHC (major histocompatibility complex). Chairman: G.

Klein, Sweden; M. Feldman, Israel.

T-Lymphocytes--antigen receptors and effector functions. Chairman: B. Cinader, Canada; E. Mozes, Israel.

Immunology and immunomanipulation of tumors. Chairman: A.L. de Weck, Switzerland; I.P. Witz, Israel.

Organization and regulated expression of immunoglobulin genes. Chairman: K. Rajewsky, West Germany; R.

Laskov, Israel.

T- and B-cells--surface markers, regulation, and differentiation. Chairman: J.B. Natvig, Norway; M.

Schlessinger, Israel.

Gene cloning in immunology (antigens, receptors and lymphokines). Chairman: M.W. Hess, Switzerland; D.

Givol, Israel.

Autoimmune disorders and new approaches to their control. Chairman: C. Steffen, Austria; S. Fuchs,

Israel.

Colloquia

Interferons and interleukin II. Chairman: J. Shoham, Israel.

AIDS. Chairman: A.L. Loachim, US; Z. Bentwich, Israel.

Immunoregulatory circuits (idiotypes, T-cells, and surface receptors). Chairman: K. Rajewsky, West

Germany; A. Frensdorff, Israel.

Antigen presenting cells and molecular events in antigen processing. Chairman: E.R. Unanue, US; R.N.

Apte, Israel.

Immune, endocrine, and neural systems--correlations and interactions. Chairman: B.D. Jankoviz, Yugo-

slavia; O. Abramsky, Israel.

Pathogenic mechanisms in autoimmunity. Chairman: J.F. Bach, France; K. Stern, Israel.

Oncogenes. Chairman: G. Klein, Sweden; Y. Becker, Israel.

Immunomodulation and immunopharmacology. Chairman: L. Chedid, France; H. Gershon, Israel.

Modern approaches to vaccination. Chairman: M.H. Van Regenmortel, France; R. Arnon, Israel.

Immunodeficiency and immunopathology. Chairman: M. Seligmann, France; Y. Shoenfeld, Israel.

Macrophages as regulators of the immune response. Chairman: M.L. Lohmann-Matthes, West Germany; A.

Gallily, Israel.

MHC-genes. Chairman: I.K. Egorov, US; C. Brautbar, Israel.

T-cell differentiation markers. Chairman: K. Hannestad, Norway; I. Schechter, Israel.

Modulation of the anti-tumor immune response. Chairman: P.J.A. Capel, The Netherlands; N. Haran-Ghara,

Israel.

Immunobiology of parasitic infections. Chairman: J.A. Louis, Switzerland; D.T. Spira, Israel.

The cell membrane and immunological functions. Chairman: M.J. Crumpton, UK; M. Wilchek, Israel.

Immunobiology of viral infections. Chairman: A.C. Allison, US; Y. Keidar, Israel.

Molecular aspects of T-cell cytotoxicity. Chairman: S.M. Hedrick, US; G. Berke, Israel.

Bone marrow transplantation. Chairman: B. Ramot, Israel; J.M. Yoffey, Israel.

Chemical aspects of macrophage functions. Chairman: A. Sulica, Romania; E. Pick, Israel.

MHC and Ig genes and their products. Chairman: B. Arnold, West Germany; E. Gagit, Israel.

B- and T-cell markers and their functions. Chairman: A. Bussard, France; H. Ben Bassat, Israel.

Human anti-tumor immune response. Chairman: J.V. Sparck, Denmark; D. Sultizeanu, Israel.

Hybridomas in basic and applied immunology. Chairman: S. Carrel, Switzerland; Z. Eshhar, Israel.

Immunopharmacology. Chairman: E. Clerici, Italy; R. Klajman, Israel.

Transplantation immunity. Chairman: J.J. van Rood, The Netherlands; E. Kedar, Israel.

Table 1 (Cont'd)

Allergic responses--triggering and mediators. Chairman: A.L. de Weck, Switzerland; I. Pecht, Israel.
 Immune regulations by interferons. Chairman: J. Vilcek, US; M. Revel, Israel.
 MHC and other antigens on the cell surface of tumor cells. Chairman: I. Green, US; U.L. Danon, Israel.
 New therapies for autoimmunity. Chairman: J. Lisowski, Poland; I.R. Cohen, Israel.
 Immunobiology of parasitic infections. Chairman: F. Ortiz, Spain; D. Gold, Israel.
 B-cell differentiation factors. Chairman: H. Metzger, US; I. Zan-Bar, Israel.

glycoprotein hormone which plays a key immunoregulatory role by inducing activation and proliferation of immunology-relevant cells in particular T lymphocytes. While still not identified *in vivo*, IL-2 has been shown to expand T-cells and to augment tumor and viral immunity in animals. Altman generated a panel of reagents in the form of chemically synthesized human IL-2 derived peptides and raised polyclonal (rabbit) or monoclonal (mouse) antibodies to intact purified recombinant IL-2 (rIL-2) or its synthetic peptide. Titration of 14 individual rabbit anti-rIL-2 sera against a panel of synthetic IL-2 peptides identified three regions (residues 14-29, 59-72, and 119-133) which constitute immunodominant domains of the molecule. Altman's studies showed that synthetic IL-2 peptides and antibodies to peptides or intact IL-2 constitute useful reagents for the detection of IL-2 in biological fluids and for analyzing the structure-function relationship of this important immunoregulatory hormone.

S. Cammiskli and A. Lanzavecchia (Preclinical Research, Sandoz Ltd., Basel, Switzerland, and Basel Institute for Immunology) have proved that the inhibition of γ -interferon and B-cell helper factors mediated by the immunosuppressant cyclosporin-A (CSA) is reversed by pure recombinant IL-2, often simultaneously with the immunosuppressant. They also found that CSA inhibits the production of γ -interferon and that exogenously provided IL-2 reverses this effect. CSA is known to be a selective inhibitor of RNA polymerase 2-dependent transcriptional ac-

tivity, and the authors postulated that IL-2 may have a regulatory role in the transcription of other genes as well.

Y. Jacques and coworkers (Institut National de la Santé et de la Recherche Medicale [INSERM] Unit 211, Faculty of Medicine, Nantes, France) reported on the modulation of anti-IL2 receptor monoclonal antibody (Mab) binding sites on a human T-cell clone by antigenic stimulation and highly purified rIL-2. The human T-cell clone was established from a rejected kidney allograft which they have studied for its ability to express IL-2 receptors upon stimulation with specific antigen and highly purified IL-2. A Mab (33B31) directed against the human IL-2 receptor has been used to quantify the density of IL-2 receptors. The results of the studies by Jacques et al. indicate that: (1) antigen and rIL-2 act in synergy to modulate the 33B31 receptor expression on a monoclonal human T-cell population, and (2) rIL-2, which is not itself able to induce the expression of 33B31 receptors, slows down the turnover of these receptors once expressed upon antigenic stimulation. Using (35 S)-labeled rIL-2, these researchers are currently investigating if high-affinity IL-2 receptors are also modulated in a similar way by antigen and rIL-2.

Studies of a potent soluble immunosuppressive factor (SUF) were reported by S. Knaan-Shanzer and D.W. van Bekkum (Radiobiological Institute, The Netherlands Organization for Applied Scientific Research, Rijswijk, The Netherlands). SUF is found in the supernatant of short-term cultures of unstimulated thymocytes or spleen cells of neonatal

rodents as well as in culture medium of hybridoma cell lines obtained by fusing neonatal mouse spleen cells with a T-lymphoma line (BW 5147). *In vitro* incubation of spleen and bone marrow cells with SUF was found to suppress an acute *in vivo* graft-versus-host reaction (in lethally irradiated mice) without affecting the hemopoietic stem cells. The addition of SUF to *in vitro* mixed lymphocyte cultures (MLC) strongly suppressed lymphocyte proliferation. The MLC suppression is exerted across the species barrier and occurs at an early stage of lymphocyte activation (within 24 hours). The expression is not due to a nonspecific inhibition of DNA synthesis (demonstrated in proliferative experiments) nor to a cytolytic effect (suppression is reversible). SUF-mediated MLC suppression is not due solely to a block in the IL-2 production, since exogenic IL-2 cannot prevent suppression. Evidence that SUF interferes with the IL-2 dependent proliferation without, however, affecting the binding of IL-2 to its receptor was obtained from experiments with the CTLL-2 cells (an IL-2 dependent cytotoxic cell line). Furthermore, *in vivo/in vitro* studies with SUF-treated rhesus monkeys showed that the binding of SUF to unstimulated peripheral blood lymphocytes (that do not express IL-2 receptor in fluorescence-activated cell sorter analysis) reduces strongly their responsiveness to mitogenic stimulus. These results suggest that SUF inhibits T-cell stimulation by interacting with a molecular structure present on the cell surface of unstimulated cells. Although distinct from the IL-2 receptor, this molecular structure may play an important regulatory role in the IL-2 dependent proliferation.

P. Orchansky, D.G. Fischer, D. Novick, and M. Rubenstein (Department of Virology, The Weizmann Institute of Science, Rehovot, Israel) have studied the effect of an N-terminal fragment of human γ -interferon (IFN- γ) prepared from the parent molecule on receptor binding and induction of human leukocyte antigen (HLA). These investigators

found that this fragment was able to compete with (125 I)-IFN- γ for binding to the IFN- γ receptor. However, it lacked at least some of the activities of IFN- γ ; namely, it had no antiviral activity and did not induce HLA antigens. Furthermore, it inhibited competitively the induction by IFN- γ of HLA-A,B,C and HLA-DR in human cells. Orchansky et al. concluded that the binding site of IFN- γ to its receptor is localized in the N-terminal one-third of the molecule. However, other parts of the polypeptide are essential for "turning-on" the receptor. The N-terminal fragment is an antagonist to IFN- γ . As such it could be potentially useful as an immunosuppressant whenever an autoimmune process is augmented by the presence of IFN- γ .

M. Fellous and F. Rosa reported on the regulation of major histocompatibility (MHC) genes by interferon (IFN). IFNs enhance cell surface levels of class I and class II MHC glycoproteins as well as human β_2 -microglobulin. This increment follows the enhancement of the corresponding messenger RNA (mRNA) content in the cytoplasm of the cell. Using isolated nuclei (which allows for the direct quantification of the transcription rates of defined genes), it was shown that IFN- β and γ enhance the transcription rate of β_2 -microglobulin and class I or A genes in a threefold to fourfold ratio after 1 hour of treatment. The enhanced transcription was maintained for at least 24 hours. These researchers also analyzed the transcription of HLA-DR genes and found that IFN- γ did not appear to modify HLA-DR gene transcription rates in different cell lines tested. They are now studying the genetic control of the IFN- γ receptor.

3 IMMUNOREGULATION

The papers in this area of research dealt essentially with immunoregulatory circuits (idiotypes, T-cells, and surface receptors). T-cells may dictate the specificity of an antibody response directly, or indirectly, in concert with antigens of anti-idiotypic molecules. T-cell mediated idiosyncrasy suppression,

which can be induced by both anti-idiotypic antibody and antigen, may relate to requirements of immunological tolerance and to somatic antibody diversification and the generation of memory.

H. Zinger, O. Axelrod, and E. Mozes (Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot, Israel) presented some of their recent studies on the nature of a T-cell line stimulated by monoclonal anti-idiotypic antibodies. This group, headed by Mozes, is one of the top immunology research groups in Israel. These researchers reported on the establishment of an IL-2 dependent T-cell line by the stimulation of T-cells with monoclonal anti-idiotypic antibodies for the investigation of the role of idiotype-anti-idiotypes in T-cell regulation. Monoclonal anti-idiotypic antibodies were prepared against (T,G)-A--L specific monoclonal antibodies (McAb 113), which were shown to express the major idiotypes of conventional anti-(T,G)-A--L antibodies of C³H-SW origin. The seven active hybridomas obtained were all of the IgM class. The resultant clones secreted antibodies which bound the stimulating homologous McAb 103 as well as conventional (T,G)-A--L specific antibodies. The latter were bound by different clones with varying efficiencies. C³H-SW mice were injected with one of the monoclonal anti-idiotypic antibodies (A-6). Ten days later, their lymph nodes were excised and a T-cell line was established and grown in the presence of IL-2 and periodic stimulation with the monoclonal anti-idiotypic antibodies. Their studies showed that stimulation with monoclonal anti-idiotypic antibodies against monoclonal (T,G)-A--L specific antibodies induced T-cell clones which are capable of responding to (T,G)-A--L.

A. Cumano and K. Rajewsky (Institute for Genetics, University of Cologne, West Germany) had shown earlier that idiotype suppression can be induced in newborn C5713L/6 mice by injection of monoclonal antibodies specific for idiotype determinants of

anti-(4-hydroxy-3-nitrophenyl) acetyl (NP) antibodies of NP-carrier conjugates. After a period of acute suppression, there follows a phase of chronic suppression in which T-cells play a regulatory role. To define the target structures for chronic suppression, these investigators sequenced mRNA from hybridomas established from normal and idiotypically suppressed animals, all producing monoclonal antibodies carrying the λ 1 light chain. The results presented showed that in the primary response which is dominated by a particular V_H and D gene, there is little somatic mutation in the antibodies and that the idiotype variability reflects largely sequence variability at the V_H-D_H and, to a lesser extent, the D_H-J_H joining regions. At the V_H-D_H border, they identified a group of four nucleotides, presumably N sequences, which are recurrently expressed, leading to the insertion of an aspartic acid residue in position 100 into a stretch of three tyrosines. This structure correlates with idiotype markers of a certain subset of antibodies which is selectively suppressed in chronic suppression. These findings suggest that the aspartic acid residues in position 100 of the heavy chain form part of the target site for idiotype T-cell recognition. Cumano and Rajewsky are now investigating the possible role of this recognition in the selection of memory cells during a secondary immune response.

M. Ran, R. Avavi, M. Efrati, S. Kort, and I.P. Witz (Department of Microbiology, the George S. Wise Faculty of Life Sciences, Tel-Aviv University, Israel) have been studying the stimulation of growth by an FC γ receptor expressing T-cell hybridoma by factors derived from H-ras transferred cells. This active group headed by Witz had postulated that FC γ receptor (FC γ R) expressed and released *in vitro* from T-cells may serve as a regulator molecule. They had previously reported that cell-free FC γ R is present in the circulation of normal animals and that the level of this circulating FC γ R increased following the inoculation of various

tumor cells into syngeneic mice. They also found that FCyR expression is increased on lymphocytes of cancer patients. In the present study, these researchers tested the possibility of a direct interaction between FCyR-expressing T-cells and malignantly transformed cells resulting in a growth stimulation of the T-cells. They found that H-ras oncogene-transformed 3T3 cells contain factors causing stimulation of growth of the T-cell hybridoma-expressing membrane and releasing cell-free FCyR. The stimulation measured by (H^3)-thymidine incorporation was found to be caused by a cytoplasmic extract, a supernatant of cell cultures or direct cell-to-cell interaction. Preliminary evidence was presented suggesting the possibility that the stimulation of the FCyR-expressing T-cell hybridoma was mediated by a factor which binds to FCyR in T-cells, a novel finding.

K. Hannestad and G. Krestoffersen (Institute of Medical Biology, University of Tromsø, Norway) and J.P. Briand (Institute of Molecular and Cellular Biology, Strasbourg, France) reported on studies of a synthetic idotype that induces helper T-lymphocytes. It is important to define the structural basis for recognition of idiotypes by T-lymphocytes in order to understand their potential role for the idotype network. These investigators have found that isolated variable (V) region light chain 315, the V λ 2 domain of BALB/c myeloma protein (M315) activates helper T-cells of BALB/c mice and that the immunogenic activity was located on a fragment consisting of sequence 88-117. In order to define the structural basis of the idotype's immunogenicity, several peptides were synthesized, all of which included CDR3 of the V λ 2-315 region. One synthetic peptide corresponding to residues 91-108 elicited helper T-lymphocytes that responded to a boost with NIP-conjugated M315 or free λ 2(315) but did not respond to NIP conjugated free λ 2(5-7). Since λ 2(315) and λ 2(5-7) only differ at positions 94, 96, and 98, it should now be possible to define which of these amino acids

have an important role in the immunogenicity and antigenic specificity of this helper T-cell inducing idotype.

C. Kieda and M. Monsigny (Center for Molecular Biophysics, Centre National de la Recherche Scientifique [CNRS], Orleans, France) reported studies of a membrane lectin of human T-suppressor cells. Human lymphocytes possess sugar-specific receptors called membrane lectins. Various subpopulations of T-lymphocytes were characterized by these investigators on the basis of their capacity to selectively bind specific neoglycoproteins. Fluorescein-labeled glycoproteins were synthesized by substitution of serum albumin with glycosylophenyl-isothiocyanate and fluorescein thiocyanate. A subpopulation of human T-lymphocytes corresponding to about 25 percent of the peripheral blood T-cells was specifically labeled by α -L-rhamnosylated fluoresceinyl thio-carbamyl serum albumin (Rha Flu BSA) and this subpopulation was isolated by an immunosorption method. Studies with these subpopulations showed that human T-suppressor cells possess a membrane lectin which specifically binds glycoconjugates containing α -L-rhamnoside.

P. Benaroch and G. Bordenave (Unit of Molecular Immunophysiology, Department of Immunology, Pasteur Institute, France) reported on a new approach for the induction of immunoglobulin allotypic suppression. Rabbit allotypic suppression is commonly induced by neonatal injections of antiallotype antibodies. These investigators have developed a powerful new method for inducing this suppression by using splenic cells from sensitized adult rabbits. The donors of these cells were sensitized by two intravenous (IV) injections of about 5×10^7 of their own peripheral blood lymphocytes coated with the appropriate IgG-carrying allotypic specificities of the a and b series. Twenty-four hours after birth, heterozygous newborns received (IV) 10^8 splenic lymphocytes from a donor sensitized against the a and b series allotypic specificities they had inherited from their father. Forty percent of the 20 young rabbits developed a

total and chronic suppression accompanied by the well-known compensatory effects due to an increased expression of the corresponding alleles. Benaroch and Bordenave showed that within the sensitized lymphocytes, the T Julius subset was responsible for the induction of this suppression. Allotypic suppression has been extensively studied in mice since 1967, always by means of antiallotype antibodies. However, it has only been possible to induce it in heterozygous F1 mice having a father of the SJL strain. In this study these investigators report for the first time Igh 1b suppression in (BALB/c X CB.20) F1 mice by using sensitized splenic lymphocytes. This new approach of the allotype suppression is important in avoiding the antibody route. Also, it provides a useful tool to investigate the cellular mechanism underlying allotypic suppression.

T. Berzins, B. Axelsson, M.L. Hammarström, S. Hammarström, and P. Perlman (Department of Immunology, University of Stockholm, Sweden) have been studying the effects of antibodies to "lymphocyte function associated antigen-1" (LFA-1) on concanavalin A (ConA) induced T-cell activation. Rabbit antibodies were produced against T-cell surface components reactive with leucoglutanin (La). By electrophoretic analysis, some of these antibodies were found to precipitate two major glycoproteins (175KD and 105KD) corresponding to LFA-1. The antibodies were not mitogenic for peripheral blood lymphocytes or T-cells but inhibited the proliferative response to ConA or to allogeneic lymphocytes in mixed lymphocyte cultures, as well as the cytotoxic effector functions in different model systems. The inhibition of the proliferative response to ConA was associated with inhibition of IL-2 production. Inhibition required the presence of the antibodies at the initiation of activation. Inhibition of T-cell proliferation by the antibodies was also associated with suppression of the expression on the T-cell surface of IL-2 receptors and of transferrin receptors as studied

by indirect immunofluorescence with the respective Mabs. The antibodies did not react with the T3 glycoprotein, indicating that LFA-1 antibodies act by inhibiting some cellular interactions required for the induction of IL-2 productions and proliferation.

4 IMMUNE, ENDOCRINE, AND NEURAL SYSTEMS

D. Cupissol, L. Garelli, H. Safdari, C. Thiery, J.B. Bureau and B. Serron (Paul Lamarque Center and Laboratory for Tumor Immunopharmacology, INSERM Unit 236, Montpellier, France) studied the relationship between cerebral cortex and cellular immunity in rats. These researchers have developed an experimental model as an approach to study the role of the cerebral cortex in the control of the immune response. Changes in immunological parameters have been reported following brain lesions (thalamus, hypothalamus, superior colliculus, and reticular formation) in experimental animal studies. Cupissol et al. have modified immunological parameters (natural killer cell [NK] activity; Mabs which characterized total T-cells, helper T-cells and suppressor T-cells; mitogen stimulation in cortectomized animals). Wistar rats were cortectomized only in the left or in the right side of the brain. Cortectomized areas included most of each cortical hemisphere. A thin margin of cortex was left intact in the parasagittal and medi-temporal basal (TS) area. Compared to sham healthy and right corectomized animals, significant modifications were observed in left cortectomized rats: decrease of NK activity; a decrease of total T-cells and helper T-cells as well as an impaired mitogen stimulation. These results suggest the existence of a relationship between the cerebral cortex and the immune system which could be mediated by hormones such as gonadal, adrenal hormones or thyroxin, insulin or thymic peptides, and is under investigation by these researchers.

L. Polic, B. Radoservic-Stasic, D. Rukavina (Department of Physiological Immunology, Medical Faculty, Ryeka,

Yugoslavia) and S.E. Fendic (Department of Endocrinology, Karolinska Institute, Stockholm, Sweden) presented an interesting report on their studies of the modulation of cellular and humoral immunity by somatostatin in mice and rats. It is well known that immune responses can be influenced by various hormones. On the other hand, changes in neurohumoral status can result from the interaction of immunocompetent cells with antigen. Hormones involved in these events are under the control of somatostatin (SRIF). This widely distributed substance has not only endocrine and paracrine capabilities but can also act as a neurotransmitter. In their studies, these researchers investigated the effects of SRIF on cellular and humoral immune responses including: (1) local graft versus host reaction (GVHR); (2) survival of allogeneic tumor transplants; (3) the effects of adoptive immunity following the treatment of donors with SRIF, and (4) the number of plaque forming cells (PFC) in spleen after the injection of xenogeneic erythrocytes. Treatment with SRIF was started either before or after the challenge with specific antigen. Control animals were injected with the same volume of saline solution or were left untreated.

The results showed that the immune processes of both types could be affected by somatostatin. Local GVHR and formation of PFC were markedly suppressive when SRIF was injected immediately after the antigen, while the primary and secondary allogeneic tumor transplants grew better in animals pretreated with SRIF. The adoptive transfer of splenocytes from SRIF treated animals which had rejected the tumor, had no effects on the survival of tumor allotransplantation of recipients. Thus, the results point to the existence of neurohumoral control of the immunity because it seems that rapid and temporary hormonal changes linked with the presence of antigens were primarily affected. However, some changes on the level of immunocytes cannot be excluded.

Studies of the controls of the immune system by dopaminergic agonists and antagonists were presented by W. Boukhris and J.P. Renillard (INSERM Unit 80, Hôpital E. Herriot, Lyon, France). Work by other investigators had shown that immune responses can be modulated by a variety of hormones and neurotransmitters, but dopamine had not been implicated among the brain messengers that may act on lymphocytes. However, in the INSERM studies, dopamine (10^{-4} to 10^{-5} M) in association with pargylene, an inhibitor of monoamine oxidase, and dihydroxy-aminotetralin (ADTN, 10^{-4} M to 10^{-5} M) markedly enhanced the *in vitro* proliferative activity of BALB/C spleen cells to ConA, but depressed thymidine incorporation induced by phytohemagglutinin (PHA) or lipopolysaccharide (LPS). These effects are inhibited by addition of dopaminergic antagonists; they cannot be demonstrated in mice younger than 3 weeks nor in aging mice (>12 months) in which a decrease in brain dopaminergic receptor expression has been documented. Treatment of adult BALB/c mice with dopaminergic antagonists (haloperidol, chlorpromazine) induces opposite alterations of the *in vitro* responses of their spleen cells: ConA-induced proliferation is decreased whereas responses to PHA and LPS are increased. Altogether, these results suggest that *in vivo*, under basal conditions, spleen lymphocyte subsets are under the control of endogenous dopamine. The competitive antagonists of D-1 receptors (flupenthixol, haloperidol, chlorpromazine) but not those of D-2 receptors (Sulpiride, Metaclopramide, Domperidone) inhibit (^3H)-thymidine incorporation induced by ConA, PHA, LPS, or allogeneic cells if added during the first hour of culture. Therefore, D-1 receptor blockade interferes with the activation and proliferation of T and B lymphocytes.

Y. Shavit, A. Depaulis, G.W. Terman, F.C. Martin, R.P. Galiane, and J.C. Liebeskind (Departments of Psychology and Medicine, University of California, Los Angeles) have recently investigated the role of opioids in modulating

NK cell activity. They found that both systemic morphine and opioid peptides released by stress suppress NK cytotoxicity in rats. Systemic administration of a quarternary analogue of morphine (N-methylmorphine), which has very little or no access into the brain, had no effect on NK activity, indicating central mediation of the morphine effect. Shavit et al. have also studied the effect of morphine given directly into the brain on NK activity. Their findings suggest that the immunosuppressive effect of systemic morphine is mediated, at least in part, via central mechanisms.

N. Mooney, S. Bowcock, and E. Cooke (Department of Medical Electronics, St. Bartholomew's Hospital, London, UK) have studied the effect of isoprenaline on subsets of peripheral blood lymphocytes. The regulation of the immune response may be influenced by the neuroendocrine system. The current study examined the *in vivo* effect of either β -adrenergic stimulation or blockade on subsets of peripheral blood mononuclear cells. The studies were carried out on healthy human subjects. The results of the study indicated that physiological activation of the adrenergic system may initiate redistribution of lymphocytes.

J. Wybran and L. Schadine (Department of Immunology, Hematology, and Transfusion, Erasme Hospital, Free University of Brussels, Belgium) presented a review, including their own studies showing that enkephalins are likely to be lymphocyte activation molecules. Recent evidence indicates that human lymphocytes as well as animal lymphocytes possess receptors for enkephalins. Furthermore, these opioid peptides may enhance T-cell mitogen responses. They will also decrease *in vitro* antibody formation. Enkephalins enhance human NK activity. This effect appears to be mediated by several mechanisms including the production of factors enhancing NK activity by lymphocytes incubated in the presence of enkephalins. The identification of these factors suggest that, at least,

interleukin-2 (IL-2) might be partially responsible for the increase in NK activity. In other experiments, enkephalins have also been shown to rapidly increase the appearance of antigens related to cell activation, such as the receptor for IL-2, the receptor for transferrin, and the receptor for active T rosettes related to cell activation. Furthermore, enkephalins enhance the percentage of cells bearing the Leu II phenotype which is related to NK cells. All these results suggest that enkephalins may be activation molecules for the T-lymphocytes as well as for the immune system and as such may represent a new class of natural biological-response modifiers as well as physiological regulators of the immune response. One of the possible impacts of these observations is that, from an immunological point of view, the stress phenomenon releases factors which are able to decrease the immune response (steroids) and activate this response (enkephalins). This suggests that any imbalance in the release of these hormones during stress may lead to stress-related diseases.

M.G. Malaise, M.G. Hazee-Hagelstien, A.M. Reuter, and P. Franchimont (University of Liège, Belgium), K. Rolla (Cilag Ltd. Technical Center Europe, Schaffhausen, Switzerland) and J. Goldstein (Ortho Pharmaceutical Corporation, Raritan, New Jersey) studied the effect of thymopentin on β -endorphin secretion *in vitro*. The basis for the study was that recent experimental data suggest a role for thymic hormones in neuro-endocrine regulation. In a short-term, double-blind study, thymopentin was shown to statistically improve several clinical parameters of patients with rheumatoid arthritis. Therefore, in the present study, these researchers tested the hypothesis that thymopentin could modulate β -endorphine secretion using rat monolayer pituitary cell cultures. They found a significant increase of β -endorphine levels upon incubation of the culture, in the presence of thymopentin. Thus, in addition to its action on immunological targets, thymopentin can act

on nonlymphoid cells and stimulate the production of isolated rat pituitary cells.

A. Morgano, I. Pierri, A. Barabino, G. Lotti, and F. Indervi (Immunology Clinic, University of Genoa, Italy) investigated the question of α -endorphin and immune responsiveness in humans. Although the presence of morphine-like receptors in human blood lymphocytes was demonstrated in 1979, their relationship with lymphocyte function is still controversial. These researchers studied the effects of α -endorphin on T-cell function by evaluating their responsiveness to several types of mitogen and measuring their blastogenesis in: (1) mixed lymphocytes reaction (MLR), (2) autologous mixed lymphocytes reactions (AMLR), and (3) non-T-T type and in AMLR of mitogen T-T type. Lymphocytes were isolated from the peripheral blood of healthy donors and T- and B-cells were separated. The α -endorphin added to the cell cultures showed an inhibitory effect on MLCR and AMLRS of up to 90 percent. Their data showed that α -endorphin has an inhibitory effect on lymphocyte functions due to a naloxone insensitive receptor.

5 IMMUNOMODULATION AND IMMUNOPHARMACOLOGY

L. Chedid (Pasteur Institute, Paris, France) presented a general view of the area of immunomodulation and immunopharmacology. A summary of his main points is presented here. Historically, immunotherapy developed in view of enhancing responses to cancer. However, today this "pro host" approach is beginning to be applied to antimicrobial immunity and to the treatment of a broader spectrum of disorders, which include autoimmunity, immune deficiencies, and even aging. Somewhat like the nervous system, the immune system has acquired the capacity of reacting to an almost unlimited number of external signals and of memorizing them. The important biotechnological progress of the past decade has reduced the com-

plexity of immunomodulation and provided investigators with an abundant armory of more precise tools such as antigenic determinants (produced by chemical synthesis or genetic engineering), host mediators or adjuvants. Thus, thymic hormones, interferons, interleukins, tumor necrosis factor, etc., are becoming available by cloning and recombinant DNA technologies. Also in current use are synthetic molecules which have been designed as any other pharmacologically active agents or as copies of microbial products such as muramyl peptides. Thus, one can expect a more rapid progress in the field than was possible during the past several years.

W.L. Olszewski and E. Zidkowska (Department of Surgical Research, Medical Research Center, Poland Academy of Science, Warsaw) and A. Engeset (Laboratory of Hematology and Lymphology, Norwegian Radium Hospital, Oslo) presented their studies on the effect of hyperthermia on local immunity in man. This study dealt with investigations of responsiveness, mitogen-presenting and stimulating properties to autologous and allogeneic lymphocytes of lymph cells harvested from hyperthermic tissues. The results of these studies showed that lymph cells harvested from tissues heated for 2 hours to 44°C acquire high stimulatory properties to allogeneics as well as autologous blood lymphocytes and reveal enhanced responsiveness to mitogens.

P. Sansoni, G. Valenti, U. Butterini (General Medical Clinic, Parma University, Italy), M.M. Khan, and E.G. Engleman (Department of Pathology and Medicine, Stanford University, California) presented their recent studies on human suppressor T-cells induced by ConA. ConA has been shown to induce peripheral lymphocytes to exert suppressive activity both in mitogen and antigen-induced lymphocyte proliferation. It was shown that the ConA-induced suppressive activity was comprised in a subset of T-lymphocytes. The aim of this study was to characterize the ConA-induced suppressor cells using a monoclonal antibody shown previously to

distinguish cytotoxic T-cells from antigen-specific suppressor T-cells. The T-cells were separated into several subsets. The results indicated that both unseparated T- and Leu 2⁺-cells showed remarkable suppressive activity, but Leu 3⁺-cells failed to demonstrate any significant suppressive effect. Furthermore, after separation and activation of Leu 2⁺ subsets all the ConA-induced suppressor cells were included in the 9.3⁺ subset. Also, a histamine type 2 receptor antagonist (cimetidine), but not a type 1 antagonist (mepyramine), almost completely prevented the induction of suppressor cells. These data together with previous results on antigen-specific and histamine-induced suppressor cells indicate that ConA-induced suppressor cells are derived from a precursor pool that is phenotypically different from cells that give rise to cytotoxic T-cells.

I. Florentin, V. Chung, G. Mathes (Hôpital Paul Brousse, Villejuf, France), J. Marai (Clinical Oncology Service, Hôpital Salpêtrière, Paris, France), and J. Martinez (Center for Pharmacology and Endocrinology, Montpellier, France) have been studying synthetic Tuftsin and analogs as exogenous immunomodulators. Tuftsin (L-thr-L-lys-L-pro-L-arg) is part of the Fc portion of a leucophilic IgG and is a stimulator of polymorphonuclear neutrophils (PMN) and macrophage phagocytic activity when cleaved from its carrier molecule. Tuftsin was shown to stimulate *in vitro* all PMN and macrophage functions which were examined through binding to cell surface receptors. In the present study, these researchers have presented further evidence that synthetic Tuftsin administered to mice could act as an immunomodulator and that its effects on immune function might be explained by a primary action on macrophages. After IV injection of 25 µg of Tuftsin per mouse, peritoneal macrophages exhibited increased phagocytic, bactericidal, and cytostatic activities as well as increased capacity to release IL-1. Con-

comitantly, antibody responses were potentiated. Lymphocyte proliferation responses to mitogens, cytolytic T-cell differentiation and IL-2 production were depressed at times at which macrophage activities were maximally enhanced. This suggests that negative regulatory functions of macrophages were also stimulated. Formylated-Tuftsin (f-thr-lys-pro-arg) and f-met-lys-pro-arg but not met-lys-pro-arg were as effective as Tuftsin in stimulating macrophage activities and this without impairing lymphocyte functions. The researchers believe that these active peptides act through binding to different receptors than Tuftsin as they did not inhibit its binding to the cell surface.

A study of the immunogenic and tumoricidal effects of Tuftsin entrapped in liposomes was presented by Z. Ergiz, E. Warner-Effratt, A. Gabizon, A.J. Treves, R. Catane (Hadassah University Hospital, Jerusalem, Israel), and M. Fridkin (The Weizmann Institute, Rehovot, Israel). Tuftsin is derived from the Fc fragment of IgG and is known to activate monocytes, macrophages, and polymorphonuclear leukocytes and to increase most of their physiological effects. In this study, these researchers entrapped Tuftsin in liposomes made of cholesterol and phosphatidylcholine in equal molar ratios and compared its activity in this form to that of free Tuftsin. Although both free Tuftsin and empty liposomes, when injected intraperitoneally in mice, caused mobilization of leukocytes and macrophages into the peritoneal cavity, the stimulating effect of liposomes containing Tuftsin was significantly greater than that of the combination of free Tuftsin and empty liposomes. In addition, the percentage of latex-ingesting cells was markedly increased in mice treated with the liposome-entrapped Tuftsin. Liposomes containing Tuftsin were also more effective than free Tuftsin in prolonging the disease-free survival and the median survival of BALB/c mice inoculated with BCL, leukemia cells. These researchers postulated that the entrapment of Tuftsin in liposomes causes the Tuftsin

to be brought more readily to the effector phagocytic cells and/or to increase its bioavailability, with consequent enhancement of its immunostimulating and tumoricidal properties.

Bo Akerström and L. Lögdberg (Department of Physiological Chemistry and Anatomy, University of Lund, Sweden) presented some of their recent work on the immunomodulating effects of α_1 -microglobulin and α_1 -microglobulin glycopeptides on human and guinea pig lymphocytes. Alpha α_1 -microglobulin (α_1 -m) is a plasma protein, earlier shown to be involved in immunity and inflammation. This glycoprotein contains two or three N-glycosidically bound oligosaccharides. Glycopeptides, containing the carbohydrate bound to asparagine plus one or two more amino acids were prepared from human α_1 -m and found to exert the immunosuppressive effect on antigen stimulations of peripheral blood lymphocytes. Both human and guinea pig α_1 -m were inhibitory on antigen-induced proliferation of guinea pig lymphocytes and similar to human α_1 -m. Glycopeptide preparations from guinea pig α_1 -m exerted the immunosuppressive effects of this homologue. Both human and guinea pig α_1 -m were found to exert direct blastogenic effects on guinea pig T-lymphocytes from regional or mesenteric lymph nodes, or purified from peritoneal exudate cells. This blastogenic effect of the protein was strain specific. Thus α_1 -m appears to be involved in lymphocyte activation, apparently mediating this function through its carbohydrate moiety. The immunomodulation by α_1 -m is evolutionarily conserved as it does not show species specificity.

Immunomodulation by methanol extraction residue of BCG tubercle bacilli (MER) has been studied by S. Ben-Efraim, D. Halperin, C. Reuben, Ch. Zimber, and D.W. Weiss (Sackler School of Medicine, Tel-Aviv University, Israel). MER is a nonspecific immunomodulator that has been tested extensively in experimental animals and cancer patients. The purpose of the present study was to define the effects of MER

on macrophage and T and B lymphocyte functions in the generation of immunologic responses in *in vitro* test systems (splenocyte cultures). The results showed that the different families of immunocytes can be variously influenced by MER in diverse test circumstances.

Studies of the protective activity of human antipeptide antibodies of *S. pyogenes* type 24 provoked by synthetic antigens was reported by L. Chedid, M. Jolivet, A. Morin, F. Parant, F. Audibert, F. Oberliny, B. Dudos, and E. Beachey (Department of Experimental Immunity, Pasteur Institute, Paris, France). In previous studies, these researchers had shown that mice vaccinated with *S. pyogenes* type 24 M protein and subsequently boosted with a synthetic peptide copying a sequence of 34 amino acids (S 34) developed high antipeptide antibody responses. In the present study, human volunteers were immunized in day 0 and 14 with the natural fragment of streptococcal M protein alone or associated with Murabutide. These volunteers subsequently received on days 60, 90, and 120 the free synthetic peptide S 34 and polymerized peptide (poly S 34). An analysis of antipeptide and anti-M protein antibody responses was made between days 90 and 140. An elevation of antipeptide antibody titers was observed in each individual tested. The antipeptide antibodies were isolated from affinity columns by pH gradient and these specific antibodies recognized natural M protein. Moreover, these antibodies incubated with *Streptococcus pyogenes* type 24 and human leukocytes were shown to be bactericidal. This is the first report showing that a synthetic peptide can be immunogenic in humans and produce a secondary response of biologically active antibodies. Using synthetic antigens for revaccination of subjects pre-sensitized by natural exposure or previous immunization could prove very useful.

K.N. Masihi, K.E. Gilbert, W. Lange (Robert Koch Institute, West Berlin) and L. Chedid (Pasteur Institute, Paris, France) have studied the conjugation of

viral subunits to muramyl-dipeptide (MDP) and their effect on influenza virus-depressed chemiluminescence (CL). A variety of virus infections are associated with a dysfunction of the phagocytic cells. Infectious influenza A as well as B viruses can considerably depress luminol-dependent CL, a sensitive indicator of the respiratory burst of phagocytic cells. Commercially available inactivated trivalent influenza whole virus, split virus, and subunit vaccines also lower CL activity. However, these researchers found that depressed CL induced by infectious influenza A virus could be elevated to normal levels when MDP was added together with a low, but not a high, dose of the virus. Profound depression of CL was induced by high doses of influenza A and B subunits. However, the same amounts of viral subunits conjugated to MDP restored or even enhanced the CL responses of spleen cells from BALB/c and C57Bl/6 mice. Splenic cells from BALB/c mice generated higher levels of CL than cells from C57Bl/6 mice. Based on these studies, Masihi et al. consider that procedures to retard the virus-induced impairment of the phagocytic cell function could have important practical implications.

A. Misifari, D. Venza Teti, V. Soto, and V. Tigano (Institute of General Physiology, University of Messina, Italy) have been studying the effect of prostaglandins (PGs) on surface immunoglobulins (SIg) of human lymphocytes. They had previously shown that exogenous PGs may affect the expression of ME, E, and Fc receptors on cell membranes of human lymphocytes while endogenous PGs do not exercise such an effect. In the present study, the effect of PGs on SIg of human B lymphocytes obtained by density gradient centrifugation was investigated. The role of endogenous PGE₂ on SIg was tested using indomethacin and meclofenamate. The results showed that both exogenous and endogenous PGs did not induce any significant change of SIg⁺ human lymphocytes as tested by immunofluorescence techniques. Also, cross linking, patch-

bing, and capping of SIg did not appear to be modified by PGs. These researchers concluded that the well-known effects of PGs on humoral immune response are not mediated at the level of SIg which serve as antigen receptors of B lymphocytes. Thus, the present and previous work by these investigators suggests that PGs may regulate the activation of B lymphocyte differentiative pathways by modulating the generation of an FcR-delivered second activating signal and without apparent effects on SIg.

Immunomodulation via the gut has been studied by S. Swinburne, I.N. Brown, and C.A. Brown (Department of Immunology, St. Mary's Hospital Medical School, London, UK). These researchers have investigated whether gut-borne mycobacteria can influence systemic antimycobacterial immune responses. CBA mice in isolator units were fed for 3 weeks with either *Mycobacterium vaccae* or *M. scrofulaceum*, two common environmental mycobacteria species, in their drinking water. After feeding, the mice were injected subcutaneously with bacillus guerinette calmet (BCG), and 50 days later their spleens were examined for their ability to proliferate *in vitro* in response to whole heat-killed mycobacteria, and to mount an enhanced primary anti-sheep erythrocyte (SE) antibody response *in vitro*. The results indicated that the parameters influencing the tested effects on spleen appeared to depend on whether the environmental species of mycobacteria persisted in the mouse tissues, the dose of BCG, and the time interval between feeding and BCG and the age of the mice used. The anti-SE responses of the spleen cells were either unaffected or enhanced. This was partly related to the age of the mice used and did not depend on the *in vitro* proliferation responses of the cells. The data clearly indicate that mycobacteria (which man is constantly ingesting in his food and water) in the gut can modulate immune responses. These researchers are currently investigating the relationship of this modulation to the development of

protective immunity against pathogenic mycobacteria.

P.F. Mühlradt, H. Tsai, and P. Conradt (Institute for Biotechnology Research, Gesellschaft für Biotechnologische Forschung, (GBF), Braunschweig, West Germany) presented an interesting report on pyocyanin modulation of T-cell response. Pyocyanin, a blue pigment produced by most strains of *Pseudomonas aeruginosa* has been known to bacteriologists for decades. However, only recently it was reported that extracts containing this compound inhibited mitogen-induced T-cell proliferation. Mühlradt et al. studied the effects of purified pyocyanin in the various steps of T-cell proliferation as well as the development and effects of cytolytic T-cells. The steps investigated were: (1) interleukin 2 (IL-2) production, (2) IL-2 receptor formation, (3) IL-2 dependent blast proliferation, (4) development, and (5) killing phase of cytolytic T-cells. The results showed that pyocyanin inhibits three of the five steps of T-cell activation (2, 4, and 5). The effects of pyocyanin were reversible as withdrawal of pyocyanin from the culture after 24 hours led to a normal, although delayed, T-cell response. The researchers consider that in view of the often serious and lengthy infection of, for example, burn patients with *Ps. aeruginosa*, liberation of pyocyanin by these bacteria in the injected areas may be one of the causes for weakened defense and may contribute to the difficulties in the treatment of these infections.

S. Corridori (Institute of Infectious Diseases, San Matteo Polyclinic, Pavia, Italy) reported on the use of an immunomodulatory compound (TPI Serono) in the treatment of acute type B-viral hepatitis. Drug addict patients affected by the virus were used in an experimental clinical trial to evaluate the influence of TPI Serono on the immunological and clinical aspects of the disease. The immunological monitoring was focused on the study and comparison of the distribution of immunocyte popu-

lations (namely, total and activated T-lymphocytes, T-helper and T-suppressor subsets, NK cells, monocytes, and macrophages) in peripheral blood as well as in liver biopsies. Monoclonal antibody techniques were used. The results showed that the thymic hormone treatment was instrumental in improving the clinical course of the disease, especially as far as the normalization of the most relevant hepatological parameters and chronicization indexes were concerned. The improvement was associated with a trend toward the re-establishment of physiological distribution values of immunocyte populations.

Histamine-induced regulation of IL-2 synthesis in man has been studied by R. Huchet (INSERM Unit 267, Villejuif, France). This study was carried out using peripheral blood lymphocytes obtained from normal individuals either on the whole population or after treatment with monoclonal anti-T_H or anti-T_S antibodies plus complement. Histamine preincubation of lymphocytes at molar concentrations of 10⁻⁶ or 10⁻⁷ led to a 50- to 90-percent reduction of IL-2 synthesis. This reduction alters the production of IL-2 by both T_H and T_S lymphocyte populations and is observed after irradiation or in the presence of prostaglandin synthesis inhibitor. Histamine preincubated lymphocytes cocultured with autologous nontreated lymphocytes inhibits the IL-2 synthesis of the latter population. This suppression was observed after treatment of the lymphocytes with anti-T_H but not after treatment with OKM1+T_H, suggesting that the induction of a suppressive activity at the T_S level requires monocytes. Conversely, no suppression was observed after treatment of lymphocytes with anti-T_S antibody. Taken together, these results suggest that histamine regulates IL-2 synthesis in normal human lymphocytes by interacting directly with IL-2 producing cells (T_H and T_S lymphocytes) and by inducing T_S suppressor cells.

I. Teoderescu-Fxareu, S. Morai, T. Negu (Department of Pathophysiology, Medicopharmaceutical Institute, Bucharest, Romania) and G. Zamfir (Victor

Babes Institute, Bucharest, Romania) reported on studies of the effect of nitrofurantoin treatment on lymphocyte antigen receptors. Studies of the action of nitrofurantoin on the membrane receptors of some cells implicated in the immune response may furnish direct information concerning the possible side effects upon the immune status during the course of therapeutical utilization of this drug (i.e., cancer treatment). It is known that the receptors for antigens in the surface of immune competent cells play a major part in triggering the humoral and cellular immune response. The present study was designed to investigate variations in the number of antigen receptors following nitrofurantoin therapy. The results showed that the animals immunized with sheep erythrocytes and treated concomitantly with nitrofurantoin in therapeutic doses did not exhibit a detectable level of lymphocyte antigen receptors, indicating that nitrofurantoin prevents the proliferation and differentiation of antigen-reactive cells implicated in the elaboration of the anti-sheep red blood cell immune response. Inhibition of the antigen receptors by nitrofurantoin also shows that treatment with this drug must be done discerningly due to its negative effect upon the cell membrane. This might affect activation, differentiation, and proliferation of immunocompetent lymphocytes bearing antigen receptors, thus lowering the capacity of producing the immune response.

M.R. Zocchi, R. Pardi, E. Ferrero, M.E. Ferrero, and C. Rugarli (San Raffaele Scientific Institute, Milan, Italy) reported on studies of the *in vivo* and *in vitro* effects of papaverine on human peripheral blood lymphocytes. Papaverine, a strong inhibitor of phosphodiesterase has been shown to inhibit *in vitro* E. rosette formation and the blastogenic response to polyclonal mitogens by producing a rise in cyclic adenosine monophosphate (cAMP) intracellular concentrations. The lack of this kind of action has also been dem-

onstrated when the drug was used on pre-activated lymphocytes. These effects were dose dependent, reversible, mitomycin C resistant, and only partly related to an inhibition of IL-2 production. Moreover, the drug *in vitro* was able to increase the percentage of lymphocytes carrying T_g and Ia-like antigens. On the other hand, the administration of papaverine to young healthy volunteers yielded similar effects on phenotypic pattern but not on lymphocyte blastogenic response. Based on these results, Zocchi et al. suggest a preferential action of papaverine on a lymphocyte subset with phenotypic and functional characteristics of suppressor cells.

The effects of cyclosporin A (CSA), prostaglandin E (PGE), and indomethacin (INDO) were studied on lectin-dependent cell-mediated cytotoxicity (LDCC) against adherent Hep-2 human carcinoma target cells by A. Perl, I. Lang, R. Gonzalez-Cabello, K. Nekam, P. Gergely, J. Feher, and J. Filip (Second Department of Medicine and Department of Physiology, Semmelweis University, Budapest, Hungary). These researchers found that while reduction of LDCC by PGE was not affected, suppression of LDCC by CSA was abrogated in the presence of INDO. In parallel experiments, CSA elicited a more than twofold increase of PGE production under LDCC assay conditions as measured by radioimmunoassay. Contrary to LDCC, depression of ConA-induced blastogenesis by CSA was not influenced by INDO, suggesting that inhibitions by CSA of LDCC and ConA-induced blastogenesis, respectively, proceed via different mechanisms.

E.H. Relyveld and B. Bizzini (Pasteur Institute, Paris, France) and S. Ben-Efraim (Sackler School of Medicine, Tel-Aviv University, Israel) presented an interesting report on their studies of antitumor low-dose chemotherapy combined with immunotherapy. The aim of this study was to find out whether the association of immunotherapy with chemotherapy would permit a decrease in the dose of drugs given to cancer patients without diminishing the effectiveness of chemotherapy. This would help minimize

the unpleasant effects of chemotherapy and significantly reduce the immunosuppressive effect of the cytostatic drugs. This treatment consisted of administering--in combination with decreasing doses of chemotherapy--externalized tumor cells (glutaraldehyde inactivated L1210 tumor cells coupled to tetanus toxoid) and an immunomodulator (*C. Granulosum*-derived P40 fraction, or Bestatin, or Azimexonour Tuftsin). The results showed that the dose of drugs (in particular daunorubicin) could be reduced at least five times while increasing the effectiveness of the combined treatment. P40 proved to be much more effective than the other immunomodulators used in this experiment.

R.J. Scheper and G.H. Boerrigter (Department of Pathology, Free University Hospital, Amsterdam, The Netherlands) have studied T-cell immunopotentialization by local application of the cytostatic drug 4-hydroxycyclophosphamide (4-HPCY). These researchers have recently developed a new protocol for potentiation of effector T-cell function. Small amounts (50 to 200 µg) of the cyclophosphamide (CY) derivative (4-HDOY) which, unlike CY, does not need liver conversion for its action--were administered intradermally shortly after contact sensitization at the site of antigen application. Contact sensitivity was markedly potentiated, as demonstrated by an increased intensity and protracted time-course of challenge reactions. Following intradermal injection, 4-HPCY rapidly percolates through the antigenically stimulated, draining lymph nodes. These researchers postulated that enhanced T-effector cell function was the result of preferential elimination of suppressor cells from these draining lymph nodes. They presented the following data in support of this view: (1) lymph node hyperplasia induced by dinitrochlorobenzene or oxazolone was further enhanced; (2) paracortical areas were preferentially enlarged; (3) 4-HPCY-treated lymph nodes showed an increased frequency of hapten-specific T effector-cells as determined by passive transfer; and (4) the

in vitro proliferative response of such lymph node-derived cells to T-cell mitogens was enhanced and to the B-cell mitogens was decreased. Apparently, important similarities exist between the effects of local 4-HPCY treatment and systemic CY-pretreatment on the immune response. As systemic treatment with a high dose of CY is known to have serious side effects, the present local protocol provides a new and versatile strategy for T-cell immunopotentialization.

6 IMMUNODEFICIENCY

C.F. Edvard Smith and L. Hammarström (Department of Chemical Immunology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden) reported on a study of patients with deficiencies in immunoglobulin A (IgA). This is the major secretory Ig. In humans, two different subclasses are produced, IgA1 and IgA2. Lack of both subclasses is the most common humoral immunodeficiency. The mechanism underlying this defect is unknown. These researchers studied patients with common variable hypogammaglobulinemia and with selective IgA deficiency. All patients had undetectable IgA in serum and saliva. One patient with IgA2 deficiency was also analyzed. Genomic DNA was digested with restriction enzymes and the presence of $\alpha 1$ and $\alpha 2$ genes was analyzed using a human α -gene probe in a Southern blotting assay. The results showed that all patients carried $\alpha 1$ and $\alpha 2$ genes in their genome even though there was undetectable IgA by standard tests. These data suggested that large gene deletions are uncommon causes of IgA deficiency. Also, digestion with BAMHI, Pst I, and Pvu II did not reveal any fragment length polymorphism in the samples studied. The use of recombinant DNA methods therefore will make it possible to eventually find the defect in these immunodeficiencies.

G.M. Mavliglit and R.E. Pollock (Departments of Clinical Immunology and Biological Therapy and General Surgery, the University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor

Institute, Houston, Texas) reported on the possibility of an etiologic factor in blood-transfusion-related acquired immune deficiency syndrome (AIDS). They reported that nearly one-third of such patients were subject to cardiac surgery requiring cardiopulmonary bypass (CPB) and hypothesized that CPB might be associated with development of severe immune dysregulation, which might predispose this subgroup to an exceptional risk of contracting blood-transfusion-related AIDS. In their study, these investigators analyzed the following: (1) T-cell subset enumerations and their ratio (T_4/T_8), and (2) T-cell function local GVHL before and during surgery, and 1 and 6 days postsurgery. The study included patients undergoing CPB and cancer resections, and patients undergoing elective, noncancer, noncardiac general procedures. The results support their hypothesis that CPB per se is associated with a profound and persistent suppression of immune function, which may render CPB patients particularly susceptible to the development of blood-transfusion-related AIDS.

J.L. Touraine (Hôpital Edward Herriot, Lyon, France) has studied the "Bare Lymphocyte Syndrome" (BLS), a condition characterized by the lack of cellular expression of HLA antigens. These antigens play a crucial role in rejection, GVHL disease and possible engraftment itself, and homing after bone marrow transplantation. Touraine studied 26 patients in Europe with BLS and the resulting immunodeficiency. The transmission is autosomal and recessive, and it is linked to genes outside chromosome 6, yet controlling the expression of HLA genes. All patients had a combined immunodeficiency which was more severe in forms with a predominant lack of expression of class I rather than class II HLA antigens. Antigen-specific cellular or humoral immune responses were virtually absent in both forms. The thymus was capable of some function but was unable to provide conditions for the development of antigen-specific recognition structures

by T-lymphocytes. Preliminary results showed that at least a partial immunological reconstitution could be obtained in these patients by transplantation of bone marrow with normal expression of HLA antigens.

D. Bohringer, W. Tiemayer, and U. Lösch (Institute for Animal Physiology, Munich, West Germany) reported on studies of avian dysgammaglobulinemia. Changes in xanthine oxidase activity, an important enzyme of purine and pteridine catabolism, has been found in various diseases, such as a decrease in hepatomass of rats or an increase during bacterial infection of liver in mice. In the present study, Bohringer et al. were able to show, for the first time, the presence of xanthine dehydrogenase (XDA) in peripheral blood lymphocytes using high pressure liquid chromatography (HPLC). The kinetic parameters of XDIT in dysgammaglobulinemic UM-B19 chicken lymphocytes showed a significantly higher activity compared to control animals. This corresponds to findings of a lower intracellular concentration of hypoxanthine, xanthine, and bipterin and a higher concentration of uric acid and isoxanthopterin in supernatants of lymphocytes from these chickens with an immunodeficiency disease. Thus, an increase of XDH activity seems to be characteristic of lymphocytes from these chickens and supports the concept that disorders of purine metabolism may be due to immunodeficiencies. Moreover, pterins participate in the control of lymphocyte formation, so an increased pteridine catabolism may lead to a disordered cell interaction.

A. Cohen and J. Barankiewicz (The Hospital for Sick Children, Division of Immunology, Research Institute, Toronto, Canada) have been studying purine nucleotides and deoxynucleotide catabolism in human thymocytes and their role in adenosine deamidase (ADA) and purine nucleoside phosphorylase (PNP) immunodeficiencies. In PNP and ADA deficiencies, the abnormalities observed in intracellular deoxynucleotide levels have been found to be more severe than in the corresponding ribose derivatives.

These observations indicate selective roles for ADA and PNP in adenine and guanine deoxynucleotide degradation as compared to the corresponding ribonucleotide catabolism. These researchers have found that distinct pathways are used for the catabolism of these purine deoxynucleotides and ribonucleotides. Thus, while adenine ribonucleotides are deaminated primarily by adenyate deaminase, adenine deoxynucleotides are exclusively deaminated by adenosine deaminase, explaining the specific impairment of adenine deoxynucleotide catabolism observed in ADA deficiency. In parallel, two distinct catabolic pathways exist for guanine nucleotide and deoxynucleotide degradation, while guanine ribonucleotide deamination proceeds primarily through guanylate reductase. Guanine deoxyribonucleotides are exclusively dephosphorylated to deoxyguanosine and then phosphorylated by PNP to guanine. These observations emphasize the importance of ADA and PNP not only in nucleotide degradation but primarily in the conversion of purine deoxyribonucleotides to their corresponding ribonucleotide derivatives through the active purine nucleoside cycles. The apparent activities of the catabolic enzymes, adenosine deaminase, adenyate deaminase and PNP as well as the purine nucleoside cycle change markedly in the course of human lymphocyte differentiation.

A study on patients with severe combined immunodeficiency (SCID) or Ty lymphocytosis was reported by R.L.H. Bolhuis, F. Smekens, R.J. van de Griend (Rotterdam Radio-Therapeutic Institute and Radio-Biological Institute, Rotterdam, The Netherlands), and B.J.M. Zegers (Department of Immunology, University Children's Hospital, Utrecht, The Netherlands). These researchers have found that mature $T_3^+T_{11}^+$ T-cells as well as $T_3^-T_{11}^+$ NK cells from peripheral blood lymphocytes (PBL) of healthy individuals can be cloned in response to lectins, IL-2 and/or stimulator or feeder cells. Lymphocytes obtained from patients with SCID as well as from patients with Ty lymphocytosis

show a strongly reduced response to mitogens and allogenic stimulator cells. Some patients with Ty lymphocytosis or with SCID show normal NK cell activity and substantial numbers of $T_3^-T_{11}^+$ lymphocytes. Bolhuis et al. have also studied the *in vitro* proliferation and functional characterization of residual $T_3^+T_{11}^+$ as well as $T_3^-T_{11}^+$ T-cells in these patients. They found that in spite of a low mitogenic response, these subsets of T-cells could be cloned and expanded from SCID and Ty lymphocytosis patients using similar culture conditions as for T-lymphocytes from normal individuals. $T_3^-T_{11}^+$ clones from new patients showed NK as well as antibody-dependent cellular cytotoxicity (ADCC) comparable to that of the clones derived from normal individuals. Their data also suggest that an imbalance may exist between $T_3^-T_{11}^+$ and $T_3^+T_{11}^+$ lymphocytes in patients with SCID.

K.M. Debatin and W.E. Brandeis (Oncology/Immunology Section, Children's Hospital, University of Heidelberg, West Germany) reported on an IL-2 receptor defect in patients with cellular immunodeficiency. Defective production of IL-2 occurs in several primary and secondary immunodeficiencies. However, defects of IL-2 receptors have not been described so far. In this study, Debatin and Brandeis reported on a boy with McKusick syndrome, which is characterized by short-limbed dwarfism and cellular immunodeficiency. At the age of 13, the patient died because of a highly malignant B-cell lymphoma of the liver. Investigations of T-cell function prior to chemotherapy showed that defective IL-2 receptors were expressed in the patient's T-cells.

IgG subclass distribution of anti-carbohydrate antibodies in normal and immunodeficient individuals was investigated by L. Hammarström, M.A.A. Persson, and C.I.E. Smith (Department of Clinical Immunology, Huddinge Hospital, Huddinge, Sweden). In normal donors, the specific antidextran, antiteichoic acid, and antipneumococcal polysaccharide antibodies were found to be mainly of the IgG2 subclass. In children, IgG1 was the

predominant subclass expressed. In IgA-deficient donors, an aberrant IgG subclass distribution patterns of specific antibodies was occasionally observed. In some of these adult donors, a preferential expression of IgG1 and IgG3 antidextran antibodies was seen, whereas in other donors anticarbohydrate antibodies were almost completely absent in spite of normal serum levels of all IgG subclasses, thus suggesting a regulatory defect more fundamental than the mere lack of IgA. In IgG2-deficient donors most anticarbohydrate antibodies were absent in serum, although low levels of anticarbohydrate antibodies could occasionally be observed. The serum antibody pattern found in these latter patients is suggestive of a non-random appearance of V gene expression.

J.S. Duke-Cohan, H. Weinberg, R. Sharm, J. Foldes, I. Leichter, N. Hussein, and D. Naor (Departments of Immunology and Orthopedics, Blood Bank and Jerusalem Osteoporosis Center, Hadassah Hospital, Hebrew University, Jerusalem, Israel) have been investigating cellular immune function in osteoporotic (OP) individuals using as indicators, the mixed lymphocyte reaction (MLR) and mitogen responsiveness. Osteoporosis is the result of an imbalance of osteoclastic and osteoblastic activity. The major regulators of osteoclastic activity appear to be of immune origin (monocytes, the prostoglandins that they secrete, and lymphocyte-released osteoclast-activating factors). In the present study, the subjects were divided into controls, borderlines, and treated and untreated osteoporotics, according to x-ray and trabecular bone density criteria. It was found that the sera of OP individuals are potent suppressors of their own MLR as well as of the MLR of unrelated individuals. The degree of suppression correlated with the extent of osteopenia. Initial results also indicate a correlation of osteopenia with expression of Ia-associated antigens on peripheral blood leukocytes, while T-cell numbers, monocyte levels, total white blood cell counts and differentials all remained

within normal limits. Lack of vitamin D or excess prostaglandin, both compounds associated with bone homeostasis, can produce an immunosuppressive effect.

A. Klein, S.M. Archer, and A. Malkin (Department of Clinical Biochemistry, Sunnybrook Medical Centre, University of Toronto, Canada) have been studying the interrelationship between cortisol and lymphocytes in newborns and patients with cirrhosis, AIDS, or cancer. It is well established that the viability of lymphocytes is dependent in part on the influence of cortisol. T-helper cells are known to be the most sensitive. Coincidentally, the ability of lymphocyte subsets to metabolize cortisol correlates inversely with their relative sensitivity to the steroid. Impaired-liver-function patients and AIDS patients have diminished T-helper/suppressor ratios, and it is suggested that cancer patients exhibit defects in immune surveillance. In this study, these researchers examined the effect of sera extract (SE) for its effect on cortisol metabolism by lymphocytes. The SE was from newborns (umbilical cord blood), patients with AIDS and cirrhosis, normal controls, and patients with cancer. It was found that the metabolism of cortisol by normal lymphocytes was significantly less in the presence of SE derived from cord blood, cirrhosis, AIDS, and cancer patients than in SE from normal controls. The results show that in clinical situations where there is a diminished T-helper/suppressor ratio and in cancer patients, there is a substance in the sera of these individuals which inhibits the metabolism of cortisol by lymphocytes which may lead to depletion of T-helper cells--the most susceptible of the T-cell subsets.

V.I. Kitvash, R.M. Schmidt and H.S. Kaufman (Medical Research Institute of San Francisco at Pacific Presbyterian Medical Center; Center for Advanced Medical Technology, San Francisco State University; and Mount Zion Hospital and Medical Center; Baloscopy Institute, San Francisco, California) presented a new approach for exploration of the nature

of immunodeficiency diseases. These investigators have studied by immunobalascopy (IBa) the global patterns of interactions among immunological parameters in patients with AIDS. IBa is a methodology and a cascade of 15 methods for detection, qualification, and simultaneous multidimensional evaluation of complex relationships between immunological parameters. IBa allows the distinction of five types of immunological imbalances, grades them by severity, and represents them as complex structures. IBa of the mean value of the absolute number of white blood cells (WBC), lymphocytes, total T-cells, B-cells, T4 and T8 cells in 11 patients with AIDS identifies a complex network of six normal (40 percent) and nine abnormal (60 percent) relationships. Abnormal relationships between immunological parameters (WBC/T4; WBC/T8; Lymph/T4; total T/T4; total T/T8; total T/B cells; B-cells/T4; B-cells/T8; T4/T8) are organized in a complex, spherically structured pattern not seen in 38 healthy controls and probably pathognomic for AIDS. These immunoregulatory mechanisms, as detectable by IBa, provide a new approach for exploring, understanding, and connecting the nature of immunodeficiency diseases.

The biological activities of serum inhibitory factors (SIF) were studied in patients with endemic (Balkan) nephropathy (EN) by Z. Ramić, D. Vehimirović, Z. Radovanović, and L.M. Lukić (Institute of Microbiology and Immunology, School of Medicine, University of Belgrade, Yugoslavia). Studies of uremic patients and of animals with experimentally induced uremia have shown that their cell-mediated immune responses are severely suppressed. These researchers have found that sera from nonuremic patients with EN contain, when compared with healthy controls, an increased level of heat-sta-

ble and noncytotoxic SIF which suppresses mitogen-induced proliferation of rat thymocytes. SIF inhibited the lectin (ConA)-triggered proliferation in a dose-dependent fashion. The degree of SIF-induced inhibition remained constant over a wide range of lectin concentrations, which indicated that inhibition did not result from SIF interaction with lectins. SIF did not change the kinetics of lectin-induced DNA synthesis during 5 days of culture. Temporal aspects of SIF-induced suppression were explored by adding SIF at various times before or after the lectins. SIF was inhibitory when acting before or within 24 hours after the lectins. However, when SIF was added 48 hours after lectins, (³H)-thymidine uptake returned to normal levels. The suppression by SIF appears to be an early, irreversible, rapid process since preincubation of thymocytes with SIF for 6 hours drastically reduced their reactivity to subsequent lectin stimulation. Thus, the immunosuppression observed in EN patients with terminal renal failure could be partially attributed to factors which affect T-cell proliferation and which appear relatively early in the course of the disease.

7 CONCLUSION

The wide range of topics covered at the Seventh European Immunology Congress as well as the high level of research reported attests to the strong commitment of European scientists to immunology research. France and Israel, with extensive research programs in all aspects of immunology research, dominated the conference in terms of the number of presentations. There were a surprising number of presentations as well as participants from countries such as Poland, Hungary and Yugoslavia, indicating that immunology research is being advocated in these countries also.

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